Tetrahedron: Asymmetry Vol. 4, No. 5, pp. 793-805, 1993
Printed in Great Britain

0957-4166/93 $6.00+.00
Pergamon Press Ltd

ENZYME-CATALYZED DESYMMETRIZATION OF *meso*-SKIPPED POLYOLS TO USEFUL CHIRAL BUILDING BLOCKS

Carlo Bonini*, Rocco Racioppi, Licia Viggiani
Dipartimento di Chimica, Università della Basilicata, Via N. Sauro 85, 85100 Potenza, Italy

Giuliana Righi, Leucio Rossi
Centro C.N.R. per lo Studio della Chimica delle Sostanze Naturali, c/o Dipartimento di Chimica,Università "La Sapienza", P.le A.Moro 5, 00185 Roma, Italy

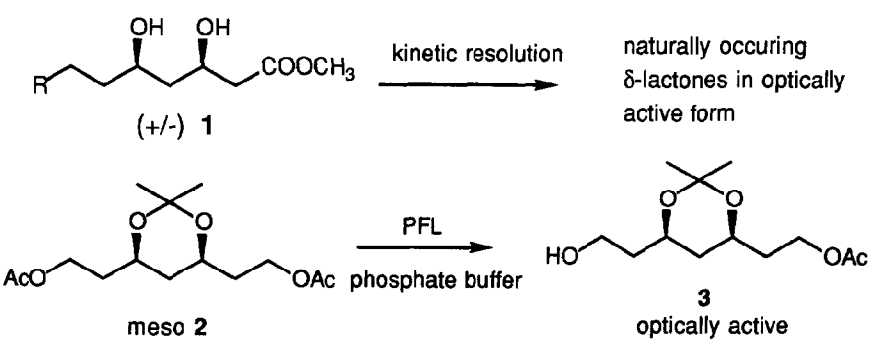
(*Received* 15 *February* 1993; *accepted* 15 *March* 1993)

Abstract: *the biocatalytic desymmetrization, in presence of different enzymes, of two models of polyfunctionalized diols in a meso form was studied* ***PFL*** *was found to be the most selective enzyme with excellent results in chemical and optical yield with some of the tested substrates. The obtained chiral building block was utilized for some useful synthetic transformations toward the synthesis of natural products*

A chemical differentiation between two enantiotopic groups in prochiral compounds has always been regarded as a major achievement.[1] The enzyme-catalyzed transformations (i.e. the transesterification in organic solvents or hydrolysis in aqueous media) have became attractive for the synthetic organic chemists to obtain chiral building blocks. In the case of meso diols good results were obtained in cyclic compounds[2] and more recently in polyhydroxylated compounds.[3] The possibility to have polyfunctionalized diols in optically active form would be extremely useful in order to increase the chiral pool.

We have recently developed (see figure 1) a biocatalytic resolution of racemic 3,5 *syn* dihydroxy esters of type **1**[4] thus obtaining, via intramolecular transesterification, the corresponding δ-lactones in optically active form. By this approach naturally occurring lactones[5], as well as mevinic acid analogs[4] have been prepared. On the same topic, in order to improve the chemical yields and to use all the starting material, we have more recently published[6] some preliminary results on the enzymatic desymmetrization of the meso *syn* 3,5 diol acetate **2** to the corresponding optically active monoacetylated compound **3**, by means of **PFL** in phosphate buffer: the enantiomeric excess (> 98 %) and the quantitative chemical yields were extremely gratifying.

Figure 1

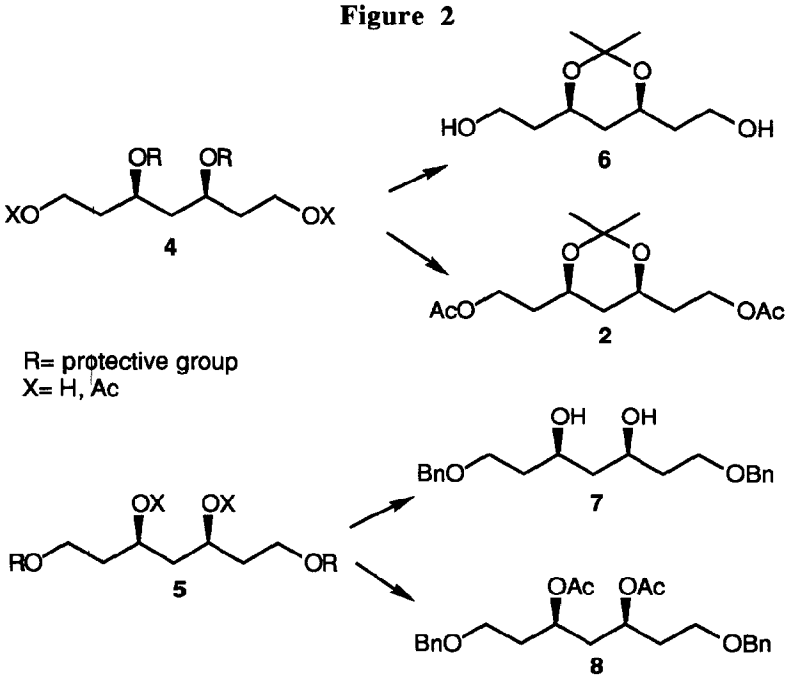


We wish to report here a more complete report of our work including the design and the preparation of model compounds as well as the results of their desymmetrization under different conditions. Also some synthetic applications of the optically active chiral building block will be outlined .

DESIGN AND PREPARATION OF THE STARTING MATERIAL

In the synthesis of natural products 1,3 polyols or skipped polyols are of great importance[7] and to this end we have been devoted for some years.[8] The possibility of obtaining a chiral fragment with a 1,3 *syn* diol structure has prompted us to design some model compounds with polyhydroxyl functions: if substrates possessing the appropriate and correct relative stereochemistry were to be available in a meso form, we thought it would be possible to differentiate between the two enantiotopic groups by enzymatic methodology. To our knowledge only two compounds possessing a 1,3 *syn* diol structure have previously been used in an enantiotopic desymmetrization.[9] We believe that the enzyme capacity should be exploited in complex substrates rather than simpler structures. Therefore , for our goal, we have chosen (see figure 2) the two seven carbon chain polyhydroxylated compounds **4** and **5**. Especially in compound **4** we were aware that the distance between the enantiotopid OX groups and the stereogenic OR centers of the molecule would challenge a positive result.

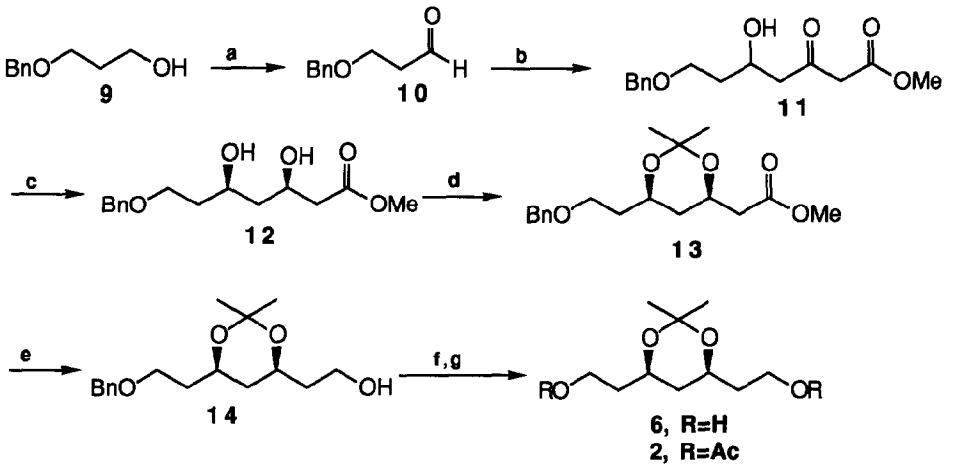
Figure 2



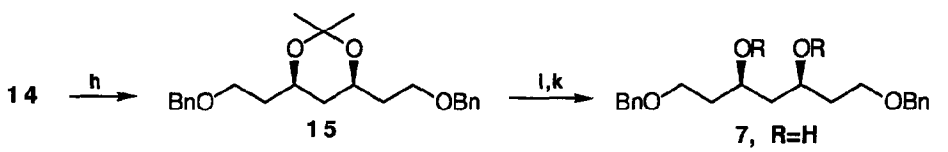
Another crucial choice was that of the protecting groups for both **4** and **5**. As demonstrated in several different systems a sterically demanding structure would be helpful for the enzyme ability, especially in the presence of five or six membered ring conformations. So we decided to protect the 1,3 *syn* diol function in compound **4** as an acetonide, while for compound **5** we used the benzyl group for the two primary hydroxyl functions. This way two possible different approaches could be tested: the transesterification in organic solvents of compounds **6** and **7** and the hydrolysis of compounds **2** and **8**.

The preparation of the starting material was achieved as described in the scheme 1. The reaction sequence, which is now being optimized, allows the final meso compounds **2**, **6**, **7** and **8** to be obtained in gram quantities and in a few days work . The only reaction which needs to be improved is the aldol condensation of aldehyde **10** with methyl acetoacetate, which gives fair yields especially with large quantities of the reagents. The diastereoselective reduction of the hydroxy ketoester **11** to the corresponding *syn* diol **12**, proceeds with the excellent diastereoselection already shown for this well known procedure.[10] Initially the acetonide protecting group caused some concern, resulting to be highly prone to rearrangement and/or hydrolysis under particular conditions. In fact the debenzylation step from compound **14** to the final diol **6**, required several attempts to be optimized, and the best results were obtained with the method described . Also traces of acid were to be avoided and when $CHCl_3$ was used for column chromatography, it was always passed through a basic allumina gel (see experimental section).

SCHEME 1



a. PCC, 78 %. **b**. CH_3COCH_2COOMe, NaH, nBuLi, 0 °C, 38%.
c.Et_3B/MeOH,$NaBH_4$, in THF, 66%. **d**. $(CH_3)_2C(OCH_3)_2$, TsOH, 95%. **e**. $LiAlH_4$,THF, 95%.**f**. Pd/C, H_2, 85%. **g**. Ac_2O, Py, 98%.



h. NaH,BnCl in THF,70 °C, 62 %. **i**. HCl, MeOH, r.t. 93%.
k. Ac_2O, Py, 98%.

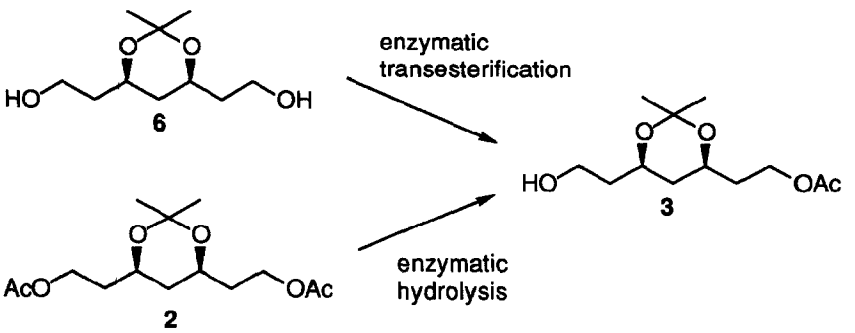
RESULTS AND DISCUSSION

For the desymmetrization reactions we have used some of the commercialy available and inexpensive enzymes which are following indicated: *Candida cylindracea lipase* (**CCL**); *Mucor javanica lipase* (**MJL**); *Pig liver esterase* (**PLE**); *Porcine pancreatic lipase* (**PPL**); *Pseudomonas fluorescens lipase* (**PFL**). Only most of the significant results obtained are reported.

Enzymatic desymmetrization of meso compounds 2 and 6

First we examined the enzymatic desymmetrization of compounds **2** and **6** (see figure 3) which would lead to the corresponding monoacetyl derivative **3** with determined absolute configuration (3R,5S, or 3S,5R).

Figure 3



The enantiomeric excess of the monoacetates can be easily determined by ^{1}H-NMR spectra in the presence of Eu(hfc)$_3$ (see experimental). The absolute configuration was determined by transformation of the chiral monoacetylated diol **3** to a known compound (see below synthetic sequences).

Enzymatic transesterification of meso diol 6.

The lipase catalyzed transesterification[11] in organic solvents with vinyl acetate was performed under different medium conditions. Table I shows the results we have obtained. Most of the enzymes gave fair enantiomeric excesses and low chemical yields with extremely long reaction times. **PFL** was indeed able to afford, in reasonable yield and reaction time, an optically pure monoacetate **3**, with the 3R,5S absolute configuration as demonstrated below; on the other hand other enzymes showed opposite enantioselectivity.

TABLE I Enzyme-catalyzed transesterification of meso diol 6

ENZYMES	solvent	reaction time	yield of 3[a]	e.e.%	$[\alpha]_D$ in $CHCl_3$	configuration
Candida cylindracea	hexane	8 d	5%	7.4	2.3	3R,5S
Pseudomonas fluorescens	Et_2O	18 h	51%[b]	>98	10.1	3R,5S
Porcine pancreatic lipase	Et_2O	24 h	24%[b]	32	-3.2	3S,5R
Porcine pancreatic lipase	THF	7 d	23%	43	-5.8	3S,5R
Porcine pancreatic lipase	dioxane	7 d	40%[b]	33	-3.8	3S,5R

a) all the yields here and elsewhere reported are intended after purification
b) some amounts (5-10%) of the diacetylated compound **2** were also obtained

Enzymatic hydrolysis of meso diacetyl compound 2

In Table II the results obtained in the biocatalytic hydrolysis of the meso substrate **2** are shown. All the reactions were performed in a 0.2M phosphate buffer solution , with a pH stat maintaining the pH value at 7 by automatic addition of 1M NaOH. The hydrolysis reactions were much faster than the corresponding transesterification with higher chemical yields. Excellent results, as already disclosed in our preliminary communication[6] were obtained by the use of **PFL**: the optical and chemical yield (almost quantitative) the reaction time and the easy procedure makes this transformation particularly attractive and likewise the reaction was performed on a 1g/scale with the same excellent results. Furthermore the chiral monoacetate **3** was shown to be the 3S,5R enantiomer of that obtained by transterification (see above) : while also **MJL** and **CCL** also showed a similar but lower ability , **PLE** did not give any appreciable results, with negligible e.e.

TABLE II. Enzyme-catalyzed hydrolysis of meso diol diacetate 2

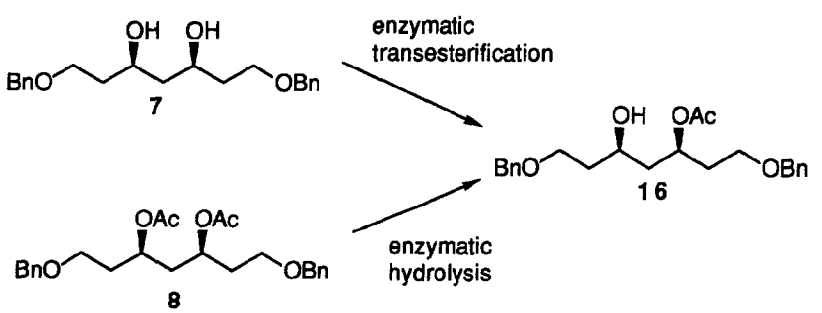
ENZYMES	reaction time	yield of 3	e.e.%	$[a]_D$ in $CHCl_3$	configuration
Candida cylindracea	*8 h*	76%	41	-4.8	3S,5R
Pig liver esterase	0.5 h	49%[a]	2.9	-	-
Mucor javanica	5 h	67%	33	-3.0	3S,5R
Pseudomonas fluorescens	5 h	98%	>98	-12.8	3S,5R

a) some amount (5-10%) of the diol **6** was also obtained

Enzymatic desymmetrization of meso compounds 7 and 8

Then we have examined the enzymatic desymmetrization of meso compounds **7** and **8** to the corresponding monoacetyl derivative **16** (see figure 4). The absolute configuration of the major enantiomer of compound **16** has not yet been determined.

Figure 4



Enzymatic transesterification of meso diol 7

The transesterification reaction on compound **7** was easily achieved, with good chemical yields (see table III for the most significant results): unfortunately no enzyme showed a good ability for the desymmetrization of the secondary skipped hydroxyl groups as was for the former substrates **2** or **6**.

Table III. Enzyme-catalyzed transesterification of meso diol 7

ENZYMES	solvent	reaction time	yield of 16	e.e.%	$[\alpha]_D$ in $CHCl_3$
Porcine pancreatic lypase	Et_2O	24 h	84%	21	2.8
Pseudomonas fluorescens	Et_2O	24 h	94%	40	3.8
Pseudomonas fluorescens	hexane	4.5 h	93%	22	2.7

Enzymatic hydrolysis of meso diol acetate 8

These hydrolysis reactions (see Table IV) appeared to be much slower with respect to those observed for compound **2**. The optical purity of the obtained monoacetate **8** did not exceed 66% e.e., again by the use of **PFL**. As shown all the enzymes gave the opposite enantiomer with respect to the transesterification reaction (see table III).

Table IV. Enzyme-catalyzed hydrolysis of meso diol acetate 8

ENZYMES	reaction time	yield of 16	e.e.%	$[\alpha]_D$ in $CHCl_3$
Pig liver esterase	24 h	5%	41	- 4.1
Pseudomonas fluorescens	2 d	12%	64	- 6.7
Porcine pancreatic lipase	3 d	5%	54	- 6.1

In conclusion a thorough investigation of the results can lead to some general considerations :

1. Compounds **2** and **6** are clearly preferred models for high enantioselective enzymatic reaction; **PFL**, both in the transesterification and in the hydrolysis (with better chemical yield) is the enzyme of choice to prepare optically pure chiral building blocks of opposite absolute configurations.
2. On the contrary compounds **7** and **8** do not seem, in our reaction conditions, good models for high enantioselective desymmetrization, although the hydrolysis gave better results but lower chemical yields.

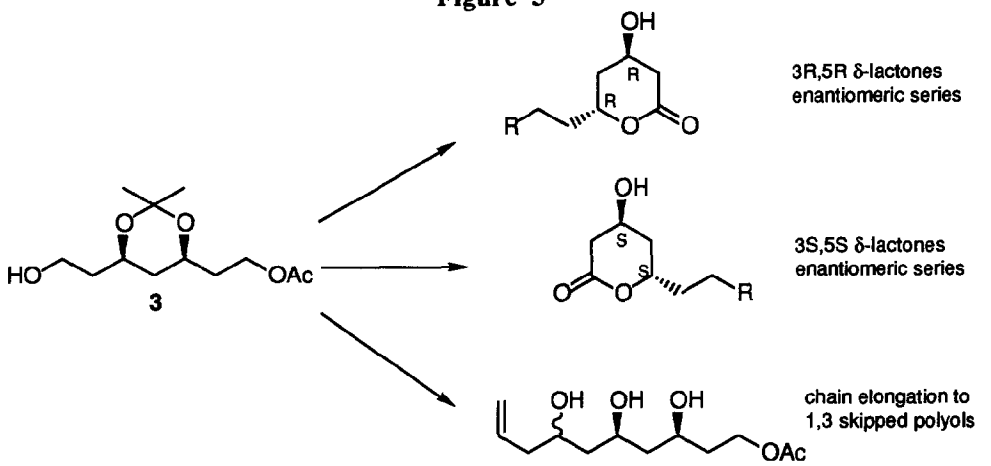
Under the reaction conditions the hydrolysis of compound **2** and the transesterification of compound **7** showed a significantly higher reactivity compared with the other compounds **6** and **8** although with different enantioselectivity.

The excellent results obtained for meso compounds **2** and **6** prompted us to expand the enzymatic desymmetrization to meso polyhydroxylated compounds possessing other substituents (i.e. like polypropionate subunits) and studies are underway in this direction.

Synthetic application of the chiral building block 3

Because of the strategic importance of chiral 1,3 *syn* diol in the synthesis of many natural products, we arranged to utilize the most abundant enantiomer of the chiral synthon 3 (obtained by hydrolysis with **PFL**, see table II) for some demonstrative application to organic synthesis as well as to determine its absolute configuration. As shown in figure 5 we planned to prepare optically active δ-lactones: by simple selective manipulation of the functional groups we could easily enter into both the 3R,5R and 3S,5S enantiomeric series. Also the chain elongation with introduction of other skipped 1,3 *syn* or *anti* polyols fragments could be one of the many possibility to utilize our seven carbon chain synthon.

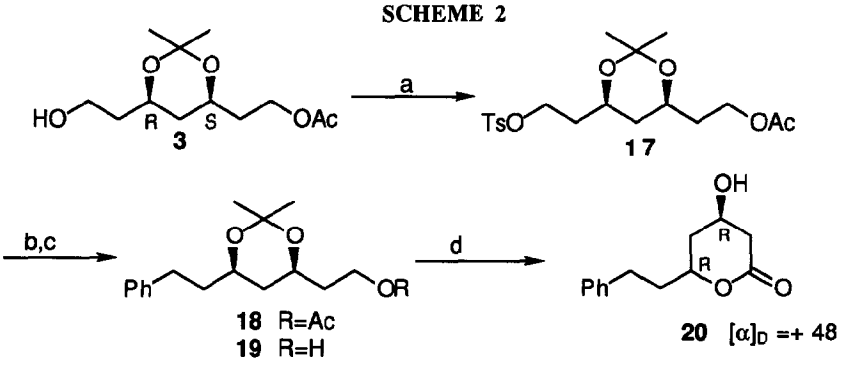
Figure 5



Preparation of the 3R,5R mevinic acid analog **20**

As already outlined in our preliminary communication[6], the transformation of the optically active compound **3** into the known mevinic acid analog **20**[8a,9b,12] (scheme 2) not only represents a first straight synthetic application, but also has firmly established the absolute configuration of the final lactone **20** (by the sign of the optical rotation) and therefore of the compound 3.

SCHEME 2



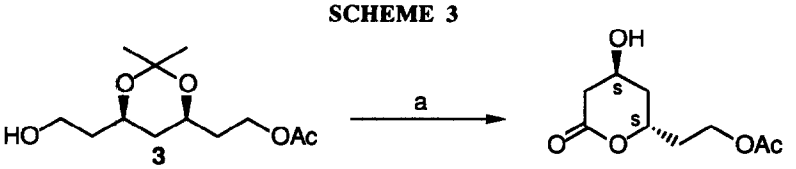
a.TsCl, Py in $CHCl_3$ (56 %);**b**. Ph_2CuLi, Et_2O, 0°C, (65 %)**c**. MeOH, Na catal. (98%)
d. $RuCl_3$,$3H_2O$,CCl_4,CH_3CN,in phosphate buffer, then pTSA (56 %).

The reaction sequence has not been optimized, but all the reactions gave good results: for the final oxidation of **19** to the lactone **20** (step **d**) a modified procedure,[13] to the original one,[14] was used in order to avoid unwanted acetonide deprotection. A stricking feature of this sequence is the potential direct coupling of the tosyl derivative **17** with any organocuprate reagent, which could allow the synthesis of all kind of 3,5 *syn* dihydroxy compounds and of the corresponding δ-lactones. A correlation to natural β-hydroxy-δ-lactones is now underway.

Preparation of the enantiomeric 3S,5S compound **21**

By opposite chain elaboration an easy entry to the other enantiomeric series (3S,5S) is opened, which again demonstrates the high potency of the chiral compound **3**.

SCHEME 3



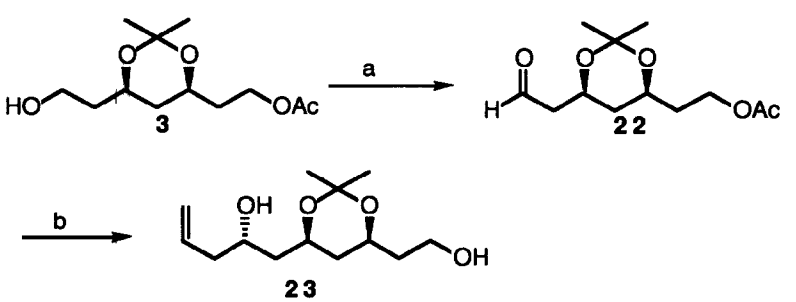
a. $RuCl_3$, $3H_2O$, CCl_4, CH_3CN in phosphate buffer, then pTSA, (66%).

21 $[\alpha]_D = -16$

Chain elongation to 1,3 skipped polyols

A first example of chain elongation of the chiral compound **3** is outlined in scheme 4. The addition of the allyl Brown reagent (-)-B-allyldiisopinocampheylborane (prepared from (-)-Ipc_2BOMe and allylmagnesium bromide)[15] to the aldehyde **22**, (prepared with the Ley's reagent)[16] led to the 3S,5R,7R tetrol **23** as the main diastereoisomer[17] (with alkaline hydrolysis of the acetyl during the work-up). Although the synthetic sequence needs to be optimized, it represents an easy and novel entry into the class of skipped polyols natural products: the use of the enantiomer (+)-$Ipc_2BCH_2CH{=}CH_2$ would lead to the corresponding all *syn* triol to be correlated to the C_1-C_{10} fragment of the macrolide antibiotic Nystatin A_1 as it has been already successfully done by Nicolaou on a quite similar compound.[18]

SCHEME 4



a. NMO, TPAOP, in CH_2Cl_2, (44%). **b.** (-)-$Ipc_2BCH_2CH{=}CH_2$, in ether, -78 °C, 48 %.

The final synthesis of this C-10 fragment of Nystatin A_1 as well as the further elaboration to polyhydroxylated compounds is in progress, which will demonstrate the remarkable usefulness of the enzyme biocatalytic transformation coupled with the classical organic synthesis.

Experimental Section

Flash chromatography was carried out on silica gel (70-230 or 230-400 mesh). TLC analyses were performed on Merck Kieselgel 60 F-254 plates. NMR spectra were registered on a Bruker AM 300, referring chemical shift values to internal $CHCl_3$.The optical rotation measurements were performed at 25 °C with a JASCO Mod. Vip/370 equipment. *Pig liver esterase* (**PLE**, EC 3.1.1.1 of type I) and crude *Porcine pancreatic lipase* (**PPL** EC 3.1.1.1 of type II) were obtained from Sigma Chemical Co. and used without further purification. *Pseudomonas fluorescens lipase* (**PFL**, EC 3.1.1.1), *Candida cylindracea lipase* (**CCL**, EC 3.1.1.3) and *Mucor javanica lipase* (**MJL**, EC 3.1.1.3) were purchased by Fluka. All the new compounds gave satisfactory elemental analytical data. The $CHCl_3$ used in chromatography was always passed through a basic allumina column in order to avoid acetonide rearrangement on the substrates.

Preparation of the Starting Materials

Compound **10** : To a stirred solution of PCC (10.783 g, 75 mmol) in 250 mL of dry CH_2Cl_2 was added 3-benzyloxy-1-propanol **9** (commercially available from Aldrich, 8.3 g, 50 mmol). After 6 h, (TLC monitoring), dry diethyl ether (250 mL) was added and the supernatant liquid was decanted from a black gum. The residue was washed with dry diethyl ether (3 x 150 mL) and the combined organic solutions were passed through a short Florisil pad and evaporated in vacuo. The crude aldehyde was purified on silica gel (petroleum ether/EtOAc 98:2 as eluent) to afford 6.27 g of pure **6** (78%). ^{1}H-NMR: 2.64 (2H, dt, J =1.7, 5.7 Hz), 3.75 (2H, t, J =5.7 Hz), 4.48 (2H, s), 7.28 (5H, bs), 9.73 ppm(1H, J =1.7 Hz). ^{13}C-NMR: 43.72, 63.74, 73.09, 127.59, 128.32, 137.78, 200.99 ppm.

Compound **11** : NaH (0.642 g, 16.06 mmol), as a mineral 60% oil dispersion, was weighed into an oven dried flask and THF (200 mL) was distilled directly into the flask . To the stirred suspension (flushed with N_2 and cooled to 0°C) were added dropwise methyl acetoacetate (1.6 mL, 14.84 mmol) and, after 10 min, n-butyllithium (1.6 M hexane solution, 9.47 mL, 15.15 mmol). After the solution became yellow, a THF solution (10 mL) of **10** (2.634 g, 16.06 mmol) was added. After TLC monitoring (15 min) the reaction was quenched with HCl 1N and extracted with EtOAc (3 x 100 mL). The combined organic layers were dried over Na_2SO_4 and the solvent evaporated in vacuo to afford crude product which was purified by flash chromatography on silica gel (petroleum ether/EtOAc 60:40) to 1.5 g of pure **11** (38 %). ^{1}H-NMR: 2.71 (2H, dd, J =3.4, 7.3 Hz), 3.32 (1H,bs), 3.49 (2H, s), 3.67 (4H, m), 3.73 (3H, s), 4.31 (1H,m), 4.51 (2H, s), 7.27-7.39 ppm (5H, br s). ^{13}C-NMR: 35.93, 49.63, 49.75, 52.30, 66.73, 67.98, 73.26, 127.66, 128.39, 137.84, 167.39, 202.74 ppm.

Compound **12** : A solution of Et_3B (2 mL of 1 M solution in THF) was added to a mixture of dry THF (15 mL) and MeOH (3.8 mL) at 25°C under N_2. After stirring for 30 min, the mixture was cooled to -65°C followed by the addition of **11** (537 mg 1.9 mmol) in THF (2 mL), and stirred for further 30 min. Then an excess $NaBH_4$ (95 mg, 2.51 mmol) was added, and the reaction was quenched after 45 min (TLC monitoring) with saturated NH_4Cl and extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over Na_2SO_4, evaporated in vacuo and then azeotroped five times with MeOH to remove boron-containing compounds. The residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc 1:1 as eluent) to afford 324 mg (66%) of *syn* methyl-(7-benzyloxy-3,5-dihydroxy)heptanoate **12**. ^{1}H-NMR: 1.5-1.9 (4H, m), 2.4-2.6 (2H, m), 3.68 (2H, m), 3.70 (3H, s), 3.82 (1H, bs), 3,9 (1H, bs), 4.01 (1H, m), 4.4 (1H, m), 4.52 (2H, s), 7.29-7.39 ppm (5H, bs). ^{13}C-NMR: 36.75, 41.60, 42.41, 51.68, 68.54, 71.46, 73.32, 127.64, 127.75, 128.44, 137.77, 172.62 ppm.

Compound **13** : Compound **12** (324 mg) was converted to the acetonide **13** by standard procedure (in 2,2-dimethoxypropane in presence of catalytic 10-camphorsulfonic acid) which was purified by silica gel chromatography (eluent $CHCl_3$/ MeOH 95:5). Compound **13** (285 mg, 95%).^{1}H-NMR: 1.36 (3H, s), 1.45 (3H,s), 1.5-1.8 (4H, m), 2.39 (1H, dd , J= 15, 6.7 Hz), 2.57 (1H, dd, J= 15, 7.5 Hz), 3.58 (2H, m), 3.69 (3H,s), 4.08 (1H,m), 4.31 (1H, m), 4.50 (2H,), 7.28-7.39 ppm (5H, bs). ^{13}C-NMR: 19.77, 30.09, 36.51, 36.62, 41.29, 51.62, 65.93, 66.14, 73.02, 98.63, 127.63, 128.39, 138.53, 171.43 ppm.

Compound **14** : To a stirred solution of **13** (1.92 g, 5.94 mmol in 50 mL of dry THF under nitrogen) $LiAlH_4$ (95%, 545.6 mg, 15.4 mmol) was slowly added at 0°C. After 1 h the mixture was quenched with MeOH, diluted with NH_4Cl and extracted with EtOAc to afford, after solvent evaporation, 1.54 g (95%) of compound **14**. ^{1}H-NMR: 1.37 (3H, s), 1.45 (3H, s), 1.6-1.85 (6H, m), 2.7 (1H, bs), 3.5-3.66 (2H, m), 3.74 (1H, m), 4.01-4.15 (1H, m), 4.49 (2H, s), 7.21-7.40 ppm (5H, bs). ^{13}C-NMR: 19.76, 30.09, 36.34, 36.68, 38.00, 60.53, 65.88, 65.98, 69.06, 72.89, 98.53, 127.48, 128.26, 138.25 ppm.

Compound **6** : Crude compound **14** (1.35 g) was debenzylated by standard procedure (Pd/C, H_2, EtOH) to afford, after 5 h, a crude mixture which was purified on silica gel ($CHCl_3$/MeOH 95:5 as eluent) to give 1.03 g of **6** (85%).^{1}H-NMR: 1.3-1.5 (2H, m), 1.37 (3H, s), 1.47 (3H, s), 2.67 (2H, bs), 3.76 (4H, m), 4.11 ppm (2H, m). ^{13}C-NMR: 19.52, 30.15, 36.46, 38.85, 60.69, 68.99, 99.71 ppm.

Compound **2** : Compound **6** (1.02 g) was acetylated by standard procedure (8.5 mL of Ac_2O in 8.5 mL of pyridine). After 1 h, the mixture was quenched with MeOH and azeotroped several times with MeOH to remove pyridine, to give 1.0 g (98%) of **2**. ^{1}H-NMR: 1.35 (3H, s), 1.41 (3H, s), 1.6-1.8 (6H, m), 2.04 (6H, s), 3.95 (2H, m), 4.15 ppm (4 H, t, J= 7.4 Hz). ^{13}C-NMR: 19.63, 20.98, 35.32, 36.87, 60.83, 65.80, 98.65, 171.06 ppm.

Compound **15** : A solution of **14** (365 mg, 1.25 mmol) in dry THF (50 mL) was stirred and refluxed at 70 °C. NaH (200 mg, 5 mmol, as a mineral 60% oil dispersion) was added and then, dropwise, benzyl chloride (0.75 mL, 5 mmol). After 18 h (TLC monitoring), the reaction was quenched with 4 mL of a saturated solution of NH_4Cl. Et_2O (25 mL) was then added, the organic layer was separated, and the acqueous layer was extracted with AcOEt (25 mL). The organic layers were washed with brine, dried over Na_2SO_4 and evaporated in vacuo to afford 612 mg of a crude mixture which was chromatographed on silica gel (petroleum ether/EtOAc 7:3 as eluent) to give 300 mg of pure **15** (62%). ^{1}H-NMR: 1.39 (3H, s), 1.45 (3H, s), 1.70-1.87 (4H, m), 3.50-3.66 (4H, m), 4.01-4.11 (2H, m), 4.52 (4H, s), 7.28-7.39 ppm (10 H, bs).^{13}C-NMR: 19.89, 30.22, 36.56, 37.14, 66.11, 66.24, 72.96, 98.46, 127.57, 128.32, 138.52 ppm.

Compound **7** : To a stirred solution of **15** (300 mg, 0.78 mmol) in MeOH (10 mL) two drops of 1M HCl were added. The reaction was monitored by TLC and stopped after 24 h by adding saturated $NaHCO_3$. Then $CHCl_3$ (50 mL) was added and the solution was filtered through a short pad of Celite to obtain 281 mg of a crude mixture. This was purified by silica gel chromatography (petroleum ether/EtOAc 7:3 as eluent) to afford 250 mg of pure **7** (93%).^{1}H-NMR: 1.49-1.63 (2H, m), 1.65-1.92 (4H, m), 3.60-3.80 (4H, m), 4.10 (2H, m), 4.53 (4H,s), 7.24-7.41 ppm (10 H, bs).^{13}C-NMR: 37.06, 43.29, 68.48, 71.60, 73.33, 127.72, 128.45, 137.98 ppm.

Compound **8** : 105 mg of **7** (0.3 mmol) were dissolved in Py (0.34 mL). Ac_2O (0.17 mL, 1.8 mmol) was then added, and the solution was stirred for 24h. The reaction was then quenched with MeOH (1 mL) and azeotroped several times with MeOH to remove pyridine, affording 129 mg of pure **8** (99%). ^{1}H-NMR: 1.8-1.95 (6H, m),1.98 (6H, s), 3.48 (4H, m),4.46 (4H, s), 5.10 (2H, m), 7.3-7.40 ppm (10H, bs).^{13}C NMR: 21.13, 34.14, 38.76, 66.37, 66.97, 72.96, 127.52, 127.64, 128.30, 138.28, 170.44 ppm.

Enzyme-catalyzed transesterification of the meso diols 6 and 7: General Procedure.

A solution of the meso diol (0.1 mmol) in 4 mL of the solvent of choice (see table I and III) was vigorously shaken at room temperature in a tightly stoppered conical flask. Vinyl acetate (172 mg, 2.0 mmol) and the chosen enzyme (4 mass eq.) were then added, and the reaction was monitored by TLC. After the suitable reaction time, the suspension was centrifugated, the supernatant decanted, and the enzyme washed with 3 mL of EtOAc and centrifugated. The organic solvents were then removed in vacuo, and the crude mixture was chromatographed (silica gel, eluent $CHCl_3$ for compound **3** and petroleum ether/EtOAc 6:4 for compound **6**) to afford monoacetyl compounds **3** and **16** in the yield reported (see tables I and III).

Enzyme-catalyzed hydrolysis of meso diol acetates 2 and 8: General Procedure

To 0.15 mmol of **2** or **8** suspended in 15 mL of a 0.2 phosphate buffer solution at pH 7.01 was added the chosen enzyme (the following amounts were employed: **CCL**, 10 mg, 360 U; **PLE**, 3 mg, 528 U; **PFL**, 15 mg, 630 U; **MJL**, 1.0 g, 5 U; **PPL**, 45 mg, 1755 U). The pH was mantained by addition of a 1 M NaOH solution, and the reaction was monitored by TLC. After the suitable reaction time, the mixture was extracted 10 times with EtOAc. The organic layers were combined, dried over Na_2SO_4 and evaporated to dryness to afford a crude mixture which was purified by silica gel chromatography (eluent $CHCl_3$ for compound **3** and petroleum

ether/EtOAc 6:4 for compound **16**) to afford monoacetyl compounds **3** and **16** in the reported yields (see tables II and IV). Note that the hydrolysis of meso compound **2** with **PFL** was performed on a 1g/scale with the same results described (see table II).

Compound **3** : ^{1}H-NMR: 1.37 (3H, s), 1.45 (3H, s), 1.65-1.83 (6H, m), 2.05 (3H, s), 3.68 (1H, bs), 3.77 (2H, m), 3.97 (1H, m), 4.16 (2H, t, J= 7.4 Hz), 4.08-4.2 ppm (1H, m). ^{13}C-NMR: 19.59, 20.82, 30.03, 35.18, 36.56, 37.97, 60.77, 60.83, 65.83, 69.25, 98.82, 171.35 ppm.

Compound **16** : ^{1}H-NMR: 1.5–1.95 (6H, m),1.99 (3H, s), 3.09 (1H, bs), 3.51 (2H, dt, J=1.7, 6.1 Hz), 3.57-3.75 (2H, m), 3.90 (1H, m), 4.48 (2H, s), 4.51 (2H, s), 5.19 (1H, m), 7.26-7.37 ppm (10H, bs).^{13}C-NMR: 21.20, 34.51, 36.31, 41.85, 66.54, 68.55, 68.95, 69.80, 63.02, 73.27, 127.54, 127.68, 128.36, 137.85, 138.22, 170.71 ppm.

Determination of the enantiomeric excess for optically active monoacetyl derivative 3.

The ee determination of **3** was based on a large difference in the ^{1}H NMR chemical shift values (for the two enantiomers) of the angular acetonide methyls in the presence (0.3-0.6 molar ratio) of the chiral shift reagent, tris[3-(heptafluoropropylhydroxymethylene)-(+)camphorato] europium, Eu(hfc)$_3$. Also the acetyl signals showed a significant difference in their chemical shift values.

Determination of the enantiomeric excess for optically active monoacetyl derivative 16.

The e.e. excess for compound **16** was determined by ^{1}H-NMR analysis in the presence of the chiral shift reagent Eu(hfc)$_3$, in a 0.3-0.6 molar ratio; the acetyl signals show a significant difference in their chemical shift values which allow an easy calculation of the integration area.

Compound **17** : Compound **3** (127 mg, 0.52 mmol) was dissolved in $CHCl_3$ (30 mL, passed through a column of basic allumina); then Py (8.5 mL) and TsCl (mg 148, 0.77 mmol) were added at 0°C. After the reaction was completed (TLC monitoring) the mixture was diluted with ether, washed with H_2O and then with saturated $NaHCO_3$. After evaporation of the dried organic layer the crude product was purified by silica gel chromatography (petroleum ether/EtOAc 75:25 as eluent) affording pure tosyl derivative **17** (117 mg, 56% yield). ^{1}H-NMR :1.25 (3H, s), 1.31 (3H, s), 1.3-1.5 (2H, m), 1.6-1.8 (4H, m), 2.03 (3H, s), 2.43 (3H, s), 3.81-3.98 (2H, m), 4.01-4.21 (4H, m), 7.3-7.4 (2H,m), 7.7-7.8 ppm (2H, m).

Compound **18** : Tosyl derivative **17** (97 mg, 0.24 mmol) was added at O°C in N_2 atmosphere, to an ether solution (15 mL) of Ph_2CuLi (1.2 mmol) prepared by standard procedure from PhLi and CuI. The reaction, was stopped after 3 h and quenched with NH_4Cl saturated solution. After extraction with ether the organic phase was dried and evaporated in vacuo affording a crude mixture. After silica gel chromatography (petroleum ether/EtOAc 9:1 as eluent) pure compound **18** (48 mg, 65 % yield) was obtained as an oil. ^{1}H-NMR: 1.39 (3H, s), 1.54 (3H, s), 1.4-1.8 (6H, m), 2.55-2.78 (2H, m), 3.79-3.95 (2H, m), 4.13 (2H, t, J= 6.7 Hz), 7.1-7.3 ppm (5H, bs). ^{13}C-NMR: 19.90, 21.13, 30.34, 31.21, 35.50, 37.12, 38.00, 61.07, 66.05, 67.79, 98.77, 125.90, 128.44, 128.70, 142.13, 171.31 ppm.

Compound **19** : Compound **18** (40 mg, 0.13 mmol) was dissolved in MeOH (3 mL) and added of catalytic Na. The stirred reaction was stopped after 4 h and the suspension was filtered and evaporated in vacuo affording the corresponding deacetylated compound **19** (35 mg, 98%). ^{13}C-NMR: 19.83, 30.22, 31.01, 36.70, 37.75, 38.04, 60.87, 67.65, 69.35, 98.65, 125.72, 128.26, 128.48, 141.89 ppm.

Compound **20** : Compound **19** (21 mg, 0.08 mmol) was dissolved in CCl_4 (0.16 mL), CH_3CN (0.16 mL), and phosphate buffer 0.2 M (0.25 mL) with vigorous stirring. Then $NaIO_4$ (50.4 mg, 0.23 mmol) was added followed by $RuCl_3/3H_2O$ (0.4 mg). The reaction was stopped after 14 h (TLC monitoring) diluting with CH_2Cl_2 (4 mL) and the organic layer was separated. The aqueous layer was then extracted with CH_2Cl_2 and the organic layers, filtered on a celite pad, were collected and dried. Then catalytic pTSA was added with stirring: after 1 h the organic solvent was evaporated and the crude mixture chromatographed on silica gel (petroleum ether/EtOAc 1:1: as eluent) affording pure **20** (10.7 mg, 56%), white solid, m.p. 75-76 °C; $[\alpha]_D$ = + 46, $CHCl_3$, c=1%.

Compound **21** : Compound **3** (15 mg, 0.061 mmol) was oxidized and then treated with pTSA with the same procedure above described for compound **20**. After purification (silica gel chromatography, $CHCl_3$/MeOH 97:3 as eluent) pure compound **21** (8 mg, 66%) was obtained. $[\alpha]_D$ = -16, $CHCl_3$, c = 0.75%. 1H-NMR: 1.8-2.1 (4H, m), 2.04 (3H, s), 2.55-2.85 (2H, m), 2.6 (1H, bs), 4.15 (1H, m), 4.21-4.41 ppm (3H, m).

Compound **22**. N-methylmorpholine-N-oxide (NMO, 160 mg, 1.36 mmol) was dissolved in CH_2Cl_2 (10 mL) containing 1g of powdered molecular sieves. To the stirred solution were added 224 mg of compound **3** (0.91 mmol) and, after 10 min, 16 mg (0.04 mmol) of tetra-n-propylammonium perruthenate (TPAP). After 0.5 h (with TLC monitoring) the reaction was diluted with CH_2Cl_2 (90 mL) and washed with sodium sulphite solution (20 mL), brine (20 mL) and saturated copper (II) sulphate solution (20 mL). After solvent evaporation, the crude mixture was chromatographed on silica gel ($CHCl_3$ as eluent) to afford 99 mg (44% yield) of pure **22**. ^{1}H NMR: 1.20 (1H, q, J=11.4 Hz), 1.30 (3H, s), 1.40 (3H, s), 1.53 (1H, dt, J= 2.63, 11.4 Hz), 1.71 (2H, m), 1.99 (3H,s), 2.43 (1H, ddd, J= 1.7, 5.3, 17.0 Hz), 2.57 (1H, ddd, J= 2.2, 7.5, 17.0 Hz), 3.89-4.00 (1H, m), 4.10 (2H, t, J= 6.6 Hz), 4.31-4.42 (1H, m), 9.72 ppm (1H, t, J= 0.44). ^{13}C-NMR: 19.52, 20.82, 29.84, 35.13, 36.47, 49.63, 60.58, 64.44, 65.56, 98.77, 170.90, 200.68 ppm.

Compound **23**. To 63.3 mg of (-)-B-methoxydiisopinocampheylborane (0.2 mmol) in dry Et_2O (5 mL) was added dropwise allylmagnesium bromide in Et_2O (1M, 0.2 mmol, 0.2 mL). The reaction mixture, after 15 min of stirring at -78°C, was brought to room temperature for 1h. Then the mixture was recooled to -78°C, and 50 mg of **22** (0.2 mmol) in 5 mL of dry Et_2O were added dropwise. After stirring for 1h (with TLC monitoring) the reaction was allowed to warm at 25°C, and then NaOH 1M (0.5 mL) and 30% H_2O_2 (1 mL) were added. The mixture was refluxed for 1h, and H_2O (10 mL) and Et_2O (10 mL) were added. The aqueous layer was extracted with Et_2O (10 mL), and the organic layers were dried over Na_2SO_4 and evaporated in vacuo to afford 69 mg of a crude mixture which was chromatographed over silica gel ($CHCl_3$ and increasing amounts of MeOH as eluent) to give **23** (23 mg, 46% yield). ^{1}H NMR: 1.40 (3H, s), 1.43 (2H,m), 1.49 (3H, s), 1.63 (2H, m), 1.74 (2H,m),, 2.24 (2H, m), 2.44 (1H, bs), 2.6 (1H, bs), 3.78 (2H, m), 3.95 (1H, m), 4.10-4.18 (1H, m), 4.18-4.28 (1H, m), 5.10 (1H, bs), 5.50 (1H, bd, J= 4.39 Hz), 5.75-5.92 ppm (1H, m). ^{13}C NMR: 19.77, 30.22, 36.38, 38.09, 41.84, 42.10, 60.83, 66.80, 67.36, 69.35, 98.84, 117.75, 134.86 ppm.

REFERENCES AND NOTES

1. For an exaustive list of references for both enzymatic or variuos chemical approaches see Hoye, T.R.; Witowski, N.E. *J. Am. Chem. Soc.*, **1992**, *114*, 7291-7292.

2. For enzymatic desymmetrization of cycloalkane or alkene diols see the following recent papers: a) Johnson, C.R.. Bis, S.J. *Tetrahedron Lett.*, **1992**, *33*, 7287-7290. b) Theil, F.; Schick, H.; Winter, G.; Reck, G. *Tetrahedron*, **1991**, *47*, 7569-7582.

3. a) Burgess, K.; Henderson, I. *Tetrahedron Lett.*, **1991**, *32*, 5701-5704 and references therein for pentitol derivatives. b) Gais, H.; Hemmerle, H.; Kossek, S. *Synthesis*, **1992**, 169-173 and references therein for other polyol derivatives.

4. Bonini, C.; Pucci, P.; Viggiani, L. *J. Org. Chem.* **1991**, *56*, 4050-4052.

5. Bonini, C.; Pucci, P.; Racioppi, R.; Viggiani, L. *Tetrahedron Asymmetry*, **1992**, *3*, 29-32.

6. Bonini, C.; Racioppi, R.; Righi, G.;Viggiani, L. *J. Org. Chem.*,**1993**, *58*, 802-803.

7. For a recent review on different methodologies to 1,3 polyols see: Oishi, T., Nakata, T. *Synthesis*, **1990**, 635-645.

8. a) Bonadies, F.; Di Fabio, R.; Gubbiotti, A.; Mecozzi, S.; Bonini, C. *Tetrahedron Lett.*, **1987**, *28*, 703-707. b) Bonini, C.; Bianco A.D.; Di Fabio, R.; Mecozzi, S.; Proposito, A.; Righi, G. *Gazz. Chim. Ital.*, **1991**, *121*, 75- 80. c) Bonini, C.; Righi, G.; Rossi, L. *Tetrahedron*, **1992**, *48*, 9801-9808.

9. a) Xie, Z.; Sakai, K. *Chem. Pharm. Bull.*, **1989**, *37*, 1650-1652. b) Johnson, C.R.; Senanayake, C.H. *J. Org. Chem.*, **1989**, *54*, 736-738.

10. Chen, K.M.; Gunderson, K.G.; Hartmann, G.E.; Prasad, K;; Repic, O.; Shapiro, M.J. *Chemistry Lett.*, **1987**, 1923-1926.

11 see for a recent review: Klibanov, A. M. *Acc. Chem. Res.* **1990**, *23*, 114-118.

12. a) Majewski, M.; Clive, D.L.J.; Anderson, P.C. *Tetrahedron Lett.* **1984**, *25*, 2101-2104. b) Roth, D.D.; Roark, W.H. *ibidem*, **1988**, *29*, 1255-12558. c) Rychnovsky, S.D.; Griesgraber, G.; Zeller, S.; Skalitzky, D.J. *J. Org. Chem.*, **1991**, *56*, 5161-5169.

13. Mori, K.; Ebata, T. *Tetrahedron*, **1986**, *42*, 4413-4420.

14 Carlsen, P.H.J.; Katsuki, T.; Martin, V.S.; Sharpless K.B. *J. Org. Chem.* **1981**, *46*, 3936-3938.

15. Jadhav, P.K.; Bhat, K.S.; Perumal, T.; Brown, H.C. *J. Org. Chem.*, **1986**, *51*, 432- 439.

16. Griffith, W.P.; Ley, S.V.; Whitecombe, G.P.; White, A.D. *J. Chem.Soc., Chem. Comm.*, **1987**, 1625 1627.

17. This is the expected stereochemical course of the Brown's reaction: for a comparative allylboration see the following reference.

18. Nicolaou, K.C.; Ahn, K.H. *Tetrahedron Lett.*, **1989**, *30*, 1217-1220.

19. This work partially supported by C.N.R. "Progetto Chimica Fine e Secondaria" and by a M.U.R.S.T. 40% grant.